EXHIBIT 3

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

- - -

IN RE: BENICAR (OLMESARTAN) PRODUCTS LIABILITY LITIGATION : MDL NO. 2606

- - -

February 7, 2017

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PROTECTED INFORMATION

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Oral expert deposition of STEPHEN M. LAGANA, M.D., taken pursuant to notice, was held at the law offices of Robins Kaplan LLP, 601 Lexington Avenue, Suite 3400, New York, New York, beginning at 10:09 a.m., on the above date, before Kimberly A. Cahill, a Federally Approved Registered Merit Reporter and Notary Public.

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EXHIBITS

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Lagana-14 2015 Paper "Immunopathogenesis of olmesartan-associated enteropathy" by Marietta, et al 305

Lagana-15 2015 Original Article "Severe intestinal malabsorption associated with olmesartan: a French nationwide observational cohort study" by Basson, et al 340

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(Deposition Exhibit No. Lagana-1, Notice of Deposition of Stephen M. Lagana, M.D., was marked for identification.)

- - -

(Deposition Exhibit No. Lagana-2, Packet of Bills from Dr. Lagana, Beginning with "Bill 9 - General", was marked for identification.)

- - -

STEPHEN M. LAGANA, M.D., after having been duly sworn, was examined and testified as follows:

- - -

EXAMINATION

- - -

BY MR. PARKER:

Q. Dr. Lagana, good morning, sir.

A. Good morning.

Q. Dr. Lagana, have you been deposed before?

A. I have not.

Q. I'm sure Mr. Slater has reviewed what this procedure is essentially all about and what will happen. Let me just say that I'm sure in the course of what will probably be a long day that I will ask you questions that are somewhat garbled. You may not understand them --

A. Okay.

Q. -- because of the inartful way in which I asked the question. If that should happen, just tell me and I'll do my best to rephrase the question.

All right?

A. Sure.

Q. And as I'm sure Mr. Slater told you, this is not an endurance contest. So to the extent you need a break, simply tell me. Provided it's not in the middle of my question, we will accommodate those breaks as needed.

Okay?

A. Yep.

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Q. Let's then start with what I have marked in front of you as Deposition Exhibit No. 1, which is the deposition notice.

Counsel has provided us last evening with some objections to those requests and with statements that certain documents would be produced, and what has been produced to me this morning are billing statements.

Is there anything else that you have brought with you today that is responsive to the deposition notice?

A. Well, I have brought this entire binder (Indicating), which includes articles from the medical literature as well as some of the reports which I have relied upon. And that would be the extent of what I've brought with me today.

Q. Fair enough. When you say reports, are you referring to reports of other experts in this litigation?

A. I am.

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Q. I see.

And are those reports of both some who have agreed to testify for the plaintiffs and some who have agreed to testify for the defense?

A. They are.

Q. And the binder that you have in front of you, you described it -- putting aside the reports -- as medical literature that you reviewed?

A. Yes.

Q. How did the literature come to you? Was it provided to you by counsel?

A. This entire binder was prepared for me by Mr. Slater and his staff. The articles within it are articles which I've provided to them primarily. There are some that they have provided to me, and there are some in here -- this binder was prepared for myself and another expert, Dr. Lebwohl, so there are some that were resultant from his work on the case.

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Q. Let me make sure I understand. Can you tell me when you received the binder?

A. I saw the binder yesterday and took possession of it today.

Q. Okay.

At the time you submitted your report, which was November 30th -- and we'll mark your report and we'll go into your report in some detail today -- did you have a collection of literature that you had reviewed for purposes of writing that report?

A. Yes.

Q. And who obtained that literature for you? Is that a result of you doing your own search or did counsel provide that literature for you?

A. I would have to estimate that about 85 percent of the papers were papers that I obtained through my own research prior to this legal matter or while preparing for this legal matter, and several of the articles were sent to

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me by counsel.

Q. And counsel being Mr. Slater or his office?

A. Uh-hum. Yes.

Q. When were you retained in that litigation?

A. I believe it was in early 2015 that we started talking.

Q. And this may be helpful. I marked as Exhibit No. 2 a collection of billing statements. Collectively, I've marked them as Exhibit No. 2. And please refer to that if that helps answer the question as to when you were retained --

A. Okay.

Q. -- approximately.

MR. SLATER: And, Bruce, obviously, I told you there are two invoices I didn't give you because they're cases he consulted in but didn't write a report, so that would be I think shielded at this point, so I just --

MR. PARKER: I didn't know

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whether that preceded --
MR. SLATER: I just want to make it clear that I did hold back two.
MR. PARKER: That's correct.
THE WITNESS: These invoices all relate to 2016, so, yeah, whatever is the earliest date in here would be approximately when we started working on these cases.
MR. PARKER: So please correct me if I'm wrong. The earliest date I see is on the first page of this exhibit, which is the billings for the general causation opinion, and that appears to be September 1, 2016.
THE WITNESS: On page 1, you're --
BY MR. PARKER:
Q. Well, this first page (Indicating), sir, of the exhibit.
A. Oh. I have a different order of documents than you do.

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Q. Mr. Slater said I would get them confused.
A. Okay.
Q. The second page, excuse me, your billings for the Block case reflect a September 1, 2016 date.
A. I agree.
Q. And just leaf through, if you would, that's the earliest date that I saw when I quickly reviewed the billings; is that correct?
(Pause.)
THE WITNESS: Yes.
BY MR. PARKER:
Q. And who, if you recall, sir, retained you? Who was the lawyer who contacted you?
A. Mr. Slater.
Q. Had you ever worked with Mr. Slater before?
A. Yes.
Q. In what type of litigation matter?
A. There was one case which I

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consulted with him on, and that was in early 2015.
Q. And what was the nature of that case?
A. It was a patient who had used olmesartan and had fairly severe side effects.
Q. So it was an olmesartan-related matter.
A. Yes.
Q. And that's the only other matter prior to your retention in September of 2016 in which you've worked with Mr. Slater?
A. Yes.
Q. Have you ever been called upon, I'll break it down, first by an attorney to address a question of whether a drug is causally related to an adverse health outcome?
MR. SLATER: You're talking about besides this litigation?
MR. PARKER: Yes, yeah.
THE WITNESS: By an

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attorney, you said.
MR. PARKER: Yes, sir.
THE WITNESS: Okay. Not that I can recall at this time.
BY MR. PARKER:
Q. Putting aside olmesartan, have you ever been asked by one or a group of medical scientists to participate in an investigation of whether a drug is causally related to an adverse health outcome?
A. I'd like you to clarify the question and the clarification I would like is, are you referring to would collaborating with colleagues on a research project be under the providence of your question?
Q. Sure. I think that's fair. Sure.
A. Okay. A specific example escapes me at the moment, but I think it's probably likely.
Q. Okay. Doctor, your billings

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in this litigation are 500 -- your rate -- excuse me -- is $500 an hour?
A. Yes.
Q. And allowing for the two cases in which you have not been disclosed, put those aside, can you look through Exhibit No. 2 and tell me whether it represents all of the billings on matters involving olmesartan for which you've been disclosed as an expert?
A. I'm sorry. May I ask for clarification again?
Q. Sure. Yes, sir. What is it?
A. Oh, you said look at bill 2 --
Q. No, Exhibit 2.
A. Oh, Exhibit 2.
Q. The whole package.
A. Okay. Got it. Got it. Got it.
Q. I just want to know whether it's reasonably complete. That's all.
A. Understood.

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(Pause.)
THE WITNESS: These bills reflect what I've submitted to Mr. Slater thus far. I've done preparation work for this deposition which I have not yet billed to Mr. Slater.
BY MR. PARKER:
Q. Approximately how many hours?
A. I would say approximately 25.
MR. PARKER: Off the record.
- - -
(A discussion off the record occurred.)
- - -
MR. PARKER: Back on the record.
BY MR. PARKER:
Q. Dr. Lagana, when you were retained by Mr. Slater, what was the -- and I'm speaking now with regard to the billing -- it's referred to as Bill 9 -

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General.
What was the question, as you recall, that you were asked to address?
A. Well, the question that was posed to me in a general sense was, Mr. Slater represented to me that he had a number of cases which could represent olmesartan enteropathy and he wanted my expert opinion on that question, to review both clinical histories as well as pathologic specimens, and to give my opinion on them. And as part of that work, a general causation statement was going to be produced.
And so that's what I understood that I would be doing and that's what I did.
Q. How do you define the term -- and how did you define it in your report -- general causation?
A. Well, I would say causation or general causation refers to, if a stimulus leads to an event, that would be

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causation; and in medicine, we apply the reasonable medical certainty threshold, which means more likely than not.
So that is the background that I used when evaluating this question.
Q. Is there a difference in your understanding between the question of general versus specific causation?
A. Yeah, I would understand them to be different insofar as, in a general case, I'm opining about the plausibility of this adverse event or, you know, if we take it away from the Benicar question and just say in general, for any stimulus, is it likely that this stimulus causes this event --
Q. In the general population?
A. I wouldn't necessarily say in the general population, because there are different -- populations can be affected by diseases differently. So, for instance, in celiac disease, gluten can affect genetically predisposed

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patients by giving them celiac disease, inflammation, villous atrophy, diarrhea, but I wouldn't say gluten in a general population causes that because, you know, 98 or 99 percent of us eat gluten with no negative effects.

So I would say plausible to the public.

Q. I just need to follow up with something. I'm not sure I understand that.

A. Sure.

Q. Let me try to approach it slightly differently. What do you understand a question of specific causation to involve?

A. For a specific causation, I would expect that we're talking about a specific case.

Q. Okay. Fair enough. Let's put that aside.

So if you're asked the question, can you arrive at an opinion as to specific causality regarding Mr. Jones

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-- making up a name -- you would understand your task to be whether or not you can determine to a reasonable degree of medical probability that olmesartan was causing some adverse event in Mr. Jones.

A. Sorry. Could you just repeat that, please?

Q. Sure. I'm trying to better understand in your mind what you understood your task to be when asked a question to assess whether olmesartan has been proven by reliable, methodologically sound, derived evidence of being a general -- a cause of sprue-like enteropathy in the general population. And that's what I'm trying to understand, how you approached that question.

A. I think maybe the term "general population" is throwing me a little bit in this context, because we know certainly plenty of people take olmesartan and do not have sprue-like enteropathy, so there is likely cofactors

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that are still being determined. They may be genetic.

So in the public at large, yes, I certainly believe olmesartan is causative of sprue-like enteropathy in some patients.

Q. And did you attempt to answer that question by looking at individual cases or did you attempt to answer that question by looking at population-based studies?

MR. SLATER: I'm just going to object to the form of the question.

You can answer.

THE WITNESS: Okay. One point that I would make before I answer your question, if I may, is that I was pretty deeply familiar with this topic before Mr. Slater called me, so that question to me was an evolution, I would say, as it should be in science. You get initial reports and then you

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investigate them more deeply and think about them more deeply.

In the case of olmesartan, I was first introduced to it through my clinical practice -- or olmesartan enteropathy, I was first introduced to it through my clinical practice.

One of the senior gastroenterologists at Columbia during one of our interdisciplinary conferences mentioned a study by Dr. Murray from the Mayo Clinic that was going to be published soon and described what -- the findings in what would soon be published as the Rubio-Tapia report in 2012 in the Mayo Clinic Proceedings.

And during that time, we started in our hospital reviewing charts of patients who had so-called seronegative celiac disease. And my clinical

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colleagues uncovered a number of cases -- I believe there were 16 cases -- of patients who were exposed to olmesartan who were classified as having seronegative celiac disease.

And so during that time, I had seen many of these by biopsies and many of the biopsies were extremely abnormal, extremely abnormal.

I can describe those cases for you if you'd like as an example or --

BY MR. PARKER:

Q. I think we'll get into it later, but for now, let's just go on.

A. Okay. And so my clinical colleagues contacted these patients and at least advised them about this new association that was described; and I can't say that I saw every follow-up biopsy, but I saw quite a few follow-up biopsies of patients who had discontinued

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olmesartan on the basis of recommendations from Columbia physicians and the degree of improvement, striking, striking.

And that affected -- you know, that certainly contributed to my thinking and it seemed to me well beyond what you could imagine would be a chance association.

And since then, I've followed the medical literature pretty closely. I read everything I see that relates to olmesartan enteropathy and I have over time certainly become more convinced that this drug does cause this syndrome in some patients.

Q. I think we'll -- I'll approach this by coming back in the context of some of the actual literature to try to better understand your method by which you've reached certain opinions.

A. Sure.

Q. First, let me follow up on what you just explained to me. When did

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this discussion occur at Columbia where you learned that the folks at Mayo were going to be publishing a case series?

A. I believe that was late 2011 or early 2012.

Q. And do you recall that the Mayo series was not published, at least on the Internet, until June of 2012?

A. I don't recall that specific timeline.

Q. We'll mark that and -- my question is, are you confident that you were made aware that he was going to publish that six months in advance of that paper being published?

A. Well -- am I confident in that. You asked for the best of my recollection of a conversation that happened four or five years ago, six years ago, so I believe, as I said, it was late 2011-early 2012. If it was, you know, March or April of 2012, I wouldn't think that that's specifically inconsistent with that recollection. So

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I -- you know, I can't give you the exact date.

Q. And the subsequent effort to go back into the chart reviews, was that precipitated by awareness that the folks at Mayo were going to publish this paper?

A. To the best of my knowledge, yes.

Q. We're going to come back to that --

A. May I just follow up on that point?

Q. Sure, absolutely.

A. You know, here, we're talking about this in the context of a litigation and also in the context of medical literature.

At the time, you know, this was -- these were patients who were essentially dying and -- or many of them were close to death, in terrible shape, and so this was a medical breakthrough that, you know, affected us -- it was a very profound effect and we were happy to

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have learned about this, not -- you know, not because, you know, I thought I'd make a few bucks billing Mr. Slater or because we'd be able to write a few papers, but, you know, this was really a dramatic change that you don't see too often in medicine.

Q. How did -- well, excuse me. Were the 16 patients that you described finding still under the active care of physicians at Columbia?

A. As a pathologist, I don't think I can answer that question terribly accurately. As I said, I saw a number of follow-up biopsies, so certainly some of them were. I couldn't give you a definite answer beyond that.

Q. For purposes of the jurors' understanding, Columbia is a referral center for people who have various forms of small bowel disease?

A. Yes.

Q. And it wouldn't surprise you if some number of these 16 came from

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outside the greater New York-New Jersey area to be examined by physicians at Columbia.

A. I would say that that is very likely.

Q. And when their treatment ends, their examination ends, they go back home, wherever they came from.

A. I believe most of them leave a phone number.

Q. Okay.

My point simply is, you're not able to tell me, for the reasons you just described right now, whether any of those 16 patients were still considered to be under the active treatment of physicians at Columbia at the time they were recontacted.

A. Well, a number of the patients were rebiopsied at Columbia, so certainly these were ongoing patient-doctor relationships if they returned to our clinic for rebiopsy.

Q. Were they asked to come back

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for a rebiopsy?

A. I wasn't there when these conversations were happening, so I'd rather -- I would only be guessing.

Q. Sure. Never want you to guess.

A. Okay.

Q. Who was the physician, if you know, who was leading the effort to do this search and call up the patients?

A. Well, we have a Celiac Disease Center with several physicians who deal with adults' complicated celiac disease, such as Dr. Peter Green, Dr. Benjamin Lebwohl, and Dr. Suzanne Lewis.

So I would say that this was probably a center-wide effort and who was actually making the phone calls, I couldn't tell you.

Q. Can you take a look -- again, going back to your billing statement, labeled "Bill 9 - General," can you tell me the approximate amount of time that it took you to actually write

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your report, the general causation report?

A. Well, it says here 7.89 hours. I would think that that reflects pretty accurately the time it took to write the actual report.

Q. Let me follow up. I mean -- let me try to be clearer.

A. Sure.

Q. I'm assuming that some of this time was spent reviewing or re-reviewing the literature and not actually drafting a report; is that accurate?

A. I see what you're saying. Well, this is the first time that I've been asked to write a general causation report and it's possible that I perhaps -- that perhaps Mr. Slater got lucky and I did not bill some of the time that I could have for reading.

I would think that --

MR. SLATER: Thanks, Bruce.

THE WITNESS: Yeah, I don't

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know -- what is the statute of limitations?
MR. PARKER: You got at least three years.
THE WITNESS: Okay.
MR. SLATER: Thanks again.
THE WITNESS: The vast majority of any of the papers that I cited in this general report, I had read previously and I had some idea of what I was looking for or what point I wanted to make and where I was getting that from.
So, you know, I didn't spend, you know, several days hermetically sealed in my office reviewing every paper again before I started writing the report. I knew what I wanted to say. This comes up in my practice and that's what I did.
But I would agree with you that perhaps I could have billed more hours for that. The 7.89

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hours here most likely represents writing time.
BY MR. PARKER:
Q. And so following up on that, none of this time then reflects time spent either telephonically or in person with Mr. Slater or other plaintiffs' lawyers talking about the evolution of your report, your general causation report.
A. Mr. Slater and I certainly had phone calls related to a couple of the cases that I can recall. A general call about my causation report, I don't recall such a conversation.
Q. Thank you.
MR. SLATER: And I just -- I've been keeping quiet a little bit, but obviously you really shouldn't be asking about our interaction that relates to a report, because that would be protected communications under the --

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MR. PARKER: I'm not going to ask about the substance, but I think I can ask --
MR. SLATER: Well, you just did, because you're talking about the report. So you're asking about conversations about the report, so that is the substance.
I didn't interrupt you, but I would just prefer that we not go any deeper into what he and I discussed with respect to his report --
MR. PARKER: I'm not going to go into the details, but I think I'm entitled to know if you met to talk about it.
MR. SLATER: I don't think actually you do, but I didn't stop you, but I think that we need to not go deeper into our interactions with regard to the report --
MR. PARKER: I'm not going

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to --
MR. SLATER: And I can assure you, I'm not going to ask questions with your experts about their interactions with lawyers. I have zero interest in that.
MR. PARKER: Well, we have a slightly different interest, but I'm not going to go into it.
BY MR. PARKER:
Q. Dr. Lagana, in the effort to prepare your general causation report, did you have discussions with other physicians or scientists?
A. I've discussed this disease and this entity with other physicians and scientists many times in the course of my practice and in the course of research, but I do not believe that I had any specific conversations related to the drafting of this report with anyone.
Q. Okay.
Doctor, when you were retained by Mr. Slater for the express

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purpose of writing a general causation report, did you understand your role to be that of an advocate or a scientist, medical scientist?
A. Scientist, absolutely.
Q. And do you think you performed that task as a scientist would?
A. Yes. And I should say, maybe if I could clarify, as a physician scientist. So I have both clinical experience and, you know, experience reading the literature. So both of those areas of expertise were brought to bear.
Q. Certainly.
Would you agree that on the essence of good science is for a scientist to look at all reliable data on a question being investigated?
MR. SLATER: Objection.
You can answer.
THE WITNESS: Well, within certain limits. It would have to be something relevant to the specific question one was

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considering.
There are tangential areas that touch any area of medicine. You can't review everything that could potentially touch something, but you do have -- I would agree that part of the scientific review is to look at the reliable, peer-reviewed literature relating to a topic at hand.
BY MR. PARKER:
Q. Good science does not involve a scientist choosing to ignore evidence which is reliable, but inconsistent with their opinion, is it? That's not good science.
MR. SLATER: Objection.
You can answer.
THE WITNESS: When there are good studies that are done that relate to the topic, I would read those studies and I would consider them whether they supported my particular point of view or did

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not; and, in fact, I would use those studies to refine my point of view or I might critique the studies to think why they could have been wrong or, as I said, I may refine my view of things.
So I do consider well -- well-done studies that are published in the peer-reviewed literature whether they are in keeping with my thinking or not.
BY MR. PARKER:
Q. And what you just described is what I think you would call a good scientific approach or a good scientific methodology.
A. I would say so.
Q. Okay.
Doctor, I want to change topics just slightly --
A. May I make one clarifying statement as well?
Q. Sure, sure.
A. In the olmesartan

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enteropathy world, I assume, you know, this is the backdrop that we're discussing these cases -- that we're discussing these questions, as far as whether or not olmesartan enteropathy exists, in the peer-reviewed medical literature, I've not seen one article that has argued that, you know, Rubio-Tapia was wrong or that this was a spurious association.
I am aware of some of the -- you know, the ROADMAP study and the follow-up study and we can get into those in more depth if and when you want to; but before -- honestly, before reading the defense expert reports, I had not either read in the peer-reviewed literature any argument against this entity, nor in innumerable discussions with gastroenterologists and gastrointestinal pathologists, no one has expressed skepticism about whether or not this is a thing.
MR. PARKER: Okay. Move to

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strike.
BY MR. PARKER:
Q. Doctor, do you recognize the difference between saying A is associated with B and A is causing B?
MR. SLATER: Objection to the form.
You can answer.
THE WITNESS: Well, there are differences in -- there are causal associations, so something can be spuriously associated or it can be causally associated.
BY MR. PARKER:
Q. So simply saying that A is associated with B does not in and of itself mean A is causing B in medical science. Agree?
A. When you determine that there is an association, when you determine that A is associated with B, that's the first step in discovery and you have additional work to do to prove that A is causing B.

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Q. All right. So finding an association is the first step.
A. Uh-hum.
Q. But it is not all that is required before you can pronounce to a degree of reasonable probability from a scientific perspective that you have proven causality. Would you agree?
A. Yeah, I think that's fairly uncontroversial.
Q. Have you had any new papers published since the C.V. that was given to us in November of 30th?
A. May I review that C.V.?
Q. Sure, yeah.
A. Is it in here?
MR. SLATER: Hopefully.
THE WITNESS: Okay.
MR. SLATER: I think it's the back of your report. It's a two-sided copy.
THE WITNESS: Okay.
MR. SLATER: Oh, you know what? I don't think his C.V.'s

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attached to that copy. He doesn't have a copy of the report with a C.V. on it.
MR. PARKER: I have a report, but no C.V.
BY MR. PARKER:
Q. Have you published any papers in the last couple months?
MR. SLATER: I might have his C.V. if you want him to look at it --
MR. PARKER: If it'll help him to answer the question.
MR. SLATER: I'm not going to mark this copy because it's got my notes all over it --
MR. PARKER: That's fine.
MR. SLATER: Do you want to see it?
THE WITNESS: Sure.
MR. SLATER: Go ahead.
(Pause.)
THE WITNESS: Okay. And the one that you have is up to date as

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of November --
MR. PARKER: 30th.
THE WITNESS: -- 30th, 2016. Do you have "Whole exome sequencing identifies a homozygous POLG2 missense" --
MR. PARKER: I didn't memorize your C.V. I couldn't tell you.
THE WITNESS: So there's one additional study that's a case report completely unrelated to this case. It's a -- it was an infant who had a rare genetic mutation.
BY MR. PARKER:
Q. Let me rephrase the question, maybe make it more pointed and helpful: Have you published anything since November 30th that's relevant to olmesartan?
A. No. I have -- I would say I have a review article which is accepted and in press at Archives of Pathology

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which relates to other medications in the GI tract, but does not to the best of my recollection mention olmesartan.
Q. And you say it's a review. Is this a review of your cases that you've seen at Columbia or a review of the literature?
A. A review of the literature with one case that I saw at Columbia.
Q. And what other chemicals or drugs are the subject of your review article?
A. These are polymers which are used in renal failure patients, sevelamer, for instance, Kayexalate, and these polymers can be deposited within the GI tract; and it's a pathology-focused review aimed at helping pathologists identify these fragments when they see them.
Q. Okay. So the gist of your article is how to identify the polymer fragments --
A. Yes.

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Q. -- in the renal tract?
A. In the GI tract.
Q. GI tract. Excuse me.
A. Yeah. I don't know if that's published yet. It's accepted. It may or may not be on their website.
Q. Have you received any promotions at Columbia since November of 30th?
A. No.
Q. What is your current medical research area, if you have one?
A. I research mainly in two areas: One is small intestinal pathology and the other is liver cancer.
Q. When you say your research involves small intestinal pathology, can you be more specific as to what your research actually involves?
A. Sure. I'm interested in celiac disease and related conditions, olmesartan enteropathy being one of them. I'm interested in small intestinal transplant. I'm interested to some

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extent in small intestinal neoplasia, although that hasn't been a large focus of my time, and liver cancer, as I mentioned.
Q. And when you say research, are you doing in vitro or in vivo experiments in this area? I'm talking now about the small intestinal pathology, not the liver cancer.
A. Okay.
Q. Describe for me the type of research you're doing.
A. Mostly I do translational studies that look at clinicopathologic correlations.
Q. Okay. Meaning you're looking at your microscope of biopsy specimens taken from people.
A. Correct.
Q. Have you done animal studies?
A. I have -- yes, I have done animal studies.
Q. Describe for me the nature

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of the work that you've done with animals.
A. Fairly recently, for several investigators, I have looked at mouse models of -- let's see -- one was a colon cancer model and one was, I believe, an IBD model.
Neither of these manuscripts have been drafted yet and I would not be the primary or senior author on either of them. I'd be a collaborator. So if you want me to get too deep into the minutia of those studies, I probably would not be able to do them justice, but I think that one was a neoplastic colon cancer model and one was an inflammatory model.
Q. Do you consider yourself to be an animal pathologist?
A. No.
Q. I'm just curious, in a general sense, why you were brought in to look at pathology from a rodent model for some outcome.
A. To some extent, it's fairly

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analogous. There are subtle differences that if you were looking for -- if you were looking for a subtle variation between the human and the animal model, I think you might need someone with more specialized knowledge in the murine model.

For the basic question of is this a cancer or not, I think it's not hard for me to answer that question for them. And as to why did they contact me, I mean, you'd have to ask them that question. I guess there are clinical interactions. They found me reasonable to work with and that's why they did it.

Q. Without going into the names, are these folks also at Columbia --

A. Yes.

Q. -- who are doing the animal research?

A. Uh-hum.

Q. Okay. Do you have any research funded by the NIH?

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A. I do not.

Q. And have you ever in your medical career?

A. No.

Q. Have you done -- and you graduated in '08. Right? 2008 from medical school?

A. Uh-hum.

Q. In your eight, going on now nine, years of medical practice, have you done any in vitro experiments?

A. I did, yes, in medical school.

Q. Okay. Since leaving medical school.

A. Oh, sorry. I have again helped other researchers with cell culture models and that sort of thing.

Q. Are you the author of any published paper involving in vitro experiments?

A. Since medical school.

Q. Yes, sir.

A. Do you mind if I take another look at the C.V.?

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Q. Please, please.

MR. SLATER: You get three shots, so choose well.

MR. PARKER: Memorize it.

(Pause.)

THE WITNESS: I would say that everything I've published has involved study of human tissues.

BY MR. PARKER:

Q. Have you ever done any consulting with any pharma companies, pharmaceutical companies?

A. You're talking about paid consulting?

Q. Yes, sir. Let's start there.

A. Okay. I don't believe so.

Q. And lastly on qualifications, in the area of the small bowel disease disorders, do you consider yourself to have expertise in any particular disorders of the small bowel?

A. Well, as a pathologist with an interest in small bowel pathology, I think that I have expertise in most, if not all, of the diseases that can affect the small bowel.

And I qualify that just a little bit because there are some rare lymphomas, for instance, that affect the small bowel which I would not hold myself up as an expert on, but the vast majority of both common and uncommon diseases that we see, yes.

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MR. PARKER: Okay. We can put your C.V. aside.

- - -

(Deposition Exhibit No. Lagana-3, Rule 26 Expert Report of Stephen Lagana, M.D. Regarding General Causation, was marked for identification.)

- - -

BY MR. PARKER:

Q. Let's go on to Exhibit 3, which is a copy of your report, minus your C.V., and the statement of your

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references.
A. By the way, may I make one more clarification?
Q. Sure.
A. I may or may not at some point have received an honorarium, or maybe more than once, for doing -- doing, like, surveys for companies that manufacture antibodies used in diagnostic pathology.
So when I say, no, I don't believe that I've done any pharmaceutical consulting, I don't think that I have, but I have maybe done some of these paid surveys for companies that make antibodies.
Q. Meaning that they send you a questionnaire to fill out --
A. Yeah, or, like, an online sort of thing where I would look at pictures and say does this antibody look -- not antibodies for use in treatment of people, antibodies used for staining human tissues -- and saying, yes, this

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looks good or this doesn't look good.
And I don't exactly have a firm recollection of that. It would have been years ago, but I don't want to hold anything back.
Q. I understand.
Now, let's take a look at your report, which is Exhibit 3.
A. Okay.
Q. Does this report reflect all the opinions which you generated as of November 30th, when this was served on us, in connection with your inquiry into general causation?
A. I would say that all of my opinions makes it sound like it's a completely exhaustive document and I would not say it's an entirely exhaustive document.
Q. Well, are there specific opinions that you had as of November 30th on the question of whether olmesartan has been proven to be a cause of general causation -- excuse me -- has been proven

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to be a cause of olmesartan at the population level or general causation that are not in Exhibit No. 3?
A. I would say that this document was meant to be a concise explanation of my thinking. It wasn't meant to be exhaustive and inclusive of every thought I have on the topic, so I think probably there were opinions and thoughts that I had which were not included in the document, including some that I thought were somewhat obvious and not -- not controversial, which I didn't address directly.
Q. Is there anything specific you can think of now that gives me an example of what you would call a material opinion, if there were any, relative to the question of general causation that I would not see if I read that report? And I have.
A. Okay. I might be able to do that if you give me a few minutes to look through it.

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Q. Sure. Sure.
A. Okay.
(Pause.)
THE WITNESS: I think I would have looked to have spoken a little bit more about my own experience seeing patients with this condition, and I probably would have cited more specifically the numerous case reports that include both dechallenge and rechallenge because I think that's very powerful evidence for direct causation.
And I'm not sure if I referenced the Basson study, the French epidemiologic study, or if I did in detail, but -- it looks like I did not. I would have liked to have included that.
And those are the three that -- those are the thoughts that come to mind now. I can't say that that's absolutely everything

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I would have done differently.
BY MR. PARKER:
Q. Doctor, in your last answer, you made reference to -- you used the word "direct" causation. We have talked so far this morning about general causation and specific causation. Please define the term "direct causation."
A. When I use that term, I mean that exposure A leads to outcome B because of exposure to -- because of exposure A.
Q. And just so our language is precise, when you say leads to, that's synonymous with causes?
A. Yes.
Q. Doctor, what are the diagnostic criteria for sprue-like enteropathy associated with olmesartan use?
A. Well, it's a broad question and maybe first I can start by defining what the entity is and then we can talk about what diagnostic criteria could be

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used to make the diagnosis.
And there are different criteria, by the way, I should say, for a gastroenterologist seeing a patient in the office as compared to me as a pathologist seeing the patient's slides --
Q. Let me stop you there. Are you comfortable addressing the criteria that a gastroenterologist should be using to diagnose the condition?
A. Yes.
Q. So then let's start first with your area of specialty, pathology. What are the pathologic criteria that you need before you personally conclude that someone has sprue-like enteropathy associated with olmesartan use?
A. The specific pathologic criteria, that's not a simple question, actually, because it really -- it's a clinicopathologic diagnosis, so showing me a slide in a vacuum, I can't give you that diagnosis. I can raise that as a

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possibility and then in following up with the clinical information, certainly I can get there as the most likely cause of the pattern of injury that I see.
But I think you're asking me to describe the histologic findings in olmesartan enteropathy. Would that be -- is that a fair way to characterize your question?
Q. I'll accept that answer. It's not exactly what my question was, but let's start there and then we can go into a little bit further.
MR. SLATER: You should let him rephrase your questions. He's doing a better job. Just kidding.
THE WITNESS: Olmesartan enteropathy affects the entire gastrointestinal tract as far as we know, most prominently in the small intestine, but also prominently in the stomach and the colon.
And the way that we can

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identify that injury histologically, the most common finding, although it's not the only finding, is inflammation and that inflammation may be lymphocytic or plasmacytic -- these are different types of inflammatory cells -- and often those are the cells that are referred to as chronic inflammatory cells, and we also find acute inflammatory cells such as neutrophils.
Those cells can be distributed variably throughout -- throughout the gut and even in a certain tissue location. You might find the lymphocytes in the lamina propria. You might find them in the epithelium, so-called intraepithelial lymphocytosis, and the same can be said of the neutrophils, eosinophils, et cetera.

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And what we see as sequelae of this inflammation, we see a variable picture. The most extreme example in the duodenum or in the small intestine would be flattening of the duodenal villi -- or, actually, I should say all the small intestinal villi -- as well as potentially fibrosis of the lamina propria.

The inflammation and the fibrosis can also be seen in the stomach and the colon. There's no potential for villous atrophy in the stomach or colon because there are no villi in either the stomach or the colon.

And so, you know, these are a -- what I have described for you now are examples of what we can see. It's not everything that we can see and, in some cases, it's the most extreme example.

BY MR. PARKER:

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Q. And I don't want to cut you off. I want to make sure you -- before I follow up with you. Are you done with your answer?

A. There are additional histologic findings that I've noticed. Some patients have markedly increased crypt apoptosis, which is death of cells in a part of the tissue where they should be proliferating, not dying.

I've encountered recently a case of granulomatis inflammation associated with olmesartan enteropathy, which was new to me. I've seen crypt atrophy which resembles autoimmune enteropathy where you see a loss of the crypts. I've also seen crypt architectural distortion, such as branched crypts, which is typically seen in inflammatory bowel disease.

So I would say that there's a pretty wide range of presentations pathologically and really one needs to be aware that it exists to make the diagnosis.

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Q. A couple follow-up questions: Crypt apoptosis, is that the opposite biological effect of crypt hyperplasia?

A. That's an interesting question. No, not really. Hyperplasia refers to the structure of the crypt, so the crypt gets longer. That means hyperplastic. Crypt apoptosis refers to a specific cell within that crypt.

So you can -- although, yeah, in one sense, the crypt is growing, it's becoming hyperplastic -- sorry. I guess this (Indicating) doesn't help -- and in the other sense, the cells are dying. You can have both of those phenomena happening at the same time, both the crypt is growing, but within it, too many individual cells are dying.

Sorry. May I grab a glass of water?

Q. Sure. Please, please, absolutely.

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(Pause.)

BY MR. PARKER:

Q. Doctor, you just told me that there's a wide range of pathological presentations in someone who presents with enteropathy with a history of taking olmesartan, if I've understood correctly.

A. Yes.

Q. I want to approach it this way: Is there -- putting aside neoplastic diseases in the small bowel, okay, put that aside, is there any histopathologic findings that you see in other forms of small bowel disorders, small bowel disease, that are not seen in what you just described as sprue-like enteropathy associated with olmesartan?

A. May I ask you --

MR. SLATER: Objection -- yeah, I was going to object to the question.

BY MR. PARKER:

Q. Sure. I'm excluding neoplastic histopathology. Okay?

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A. Yep.
Q. In the context of other histopathologic changes in the small bowel, for all other entities, celiac disease, autoimmune enteropathy, collagenous sprue, unclassified sprue, irritable bowel disease, do any of them present with pathology not seen in the long list that you just gave me for sprue-like enteropathy?
A. I see. Well, many of those entities can overlap pathologically which is why clinicopathologic correlation is important in this diagnosis or necessary.
Are there some of those that would not be -- could not potentially be confused with olmesartan enteropathy? There are certainly diseases which affect the small intestine which I don't think could ever rationally or reasonably be confused with olmesartan enteropathy.
Q. Such as?
A. Certain infections, for instance.

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Q. Anything else, sir?
A. I don't think that peptic injury would be reasonably confused with sprue-like enteropathy due to olmesartan -- if you expect this to be an exhaustive list, then please give me a few more minutes to think about it.
Q. Just take a few minutes to think about it. It's important.
A. Okay.
(Pause.)
THE WITNESS: I believe that there are subtle differences between many of the entities that you've mentioned and olmesartan enteropathy which an expert, experienced GI pathologist, could pick up on; but pathognomonic, no.
BY MR. PARKER:
Q. I think what you just told me before, however, was that if I laid out in front of you pathology from patients with diagnosed celiac disease, autoimmune enteropathy, collagenous

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sprue, unclassified sprue, and someone who had enteropathy who happened to take olmesartan, you -- I think you told me you wouldn't be able to tell the difference amongst them.
MR. SLATER: Objection.
You can answer.
THE WITNESS: I wouldn't say that that's what I said. I would say that there are similarities. Certainly there would be some histologic similarities between many of those entities. There are histologic clues that I would be able to appreciate.
You know, I -- I did write a review article on this topic, which I'm sure that you read, which was aimed at helping pathologists make the diagnosis when faced with biopsies with these findings.
And certainly I would acknowledge that there is a subset

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of celiac disease patients, for instance, whose biopsies would look the same as an olmesartan enteropathy patient and even, you know, if I say I'm, you know, God's gift to GI pathology still couldn't make the distinction. But there are examples -- a fair number -- where I could.
For instance, I've noticed and others have noticed and it's in the literature, a fair percentage of the olmesartan enteropathy patients don't have the degree of intraepithelial lymphocytosis that you would expect in a celiac disease patient with flat mucosa, so if you happen to have a case of olmesartan enteropathy where the mucosa is flat, if you wanted to tell me that that's a celiac disease patient, I would say, okay, this would be a 3C, which is a more

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severe form of celiac disease, and I would expect to find copious intraepithelial lymphocytes. I have noticed in some olmesartan enteropathy patients -- and as I said, this is in the literature -- we don't necessarily find that.

So there are cases -- to get back to your question, there are cases in which I couldn't tell you the difference and cases in which I could strongly suspect one way or the other.

BY MR. PARKER:

Q. And in that review article, didn't you also say that autoimmune enteropathy is virtually undistinguishable from olmesartan or sprue-like enteropathy --

A. Histologically, I would agree with that.

Q. And we're only talking about pathology right now to be fair to you. Okay?

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A. Okay.

Q. You've also published that there is no cardinal histopathologic finding associated with or seen with patients who have sprue-like enteropathy.

MR. SLATER: Objection.

You can answer.

THE WITNESS: Yeah, I agree. You have to look at the entirety of the slide and think about all the findings and -- to actually make the diagnosis, as I've said, you need clinicopathologic correlation.

BY MR. PARKER:

Q. So let's turn now, if you're comfortable, to the GI clinical side.

A. Sure.

Q. What does a clinician have to see clinically -- and you've given me the pathologic piece of the puzzle. What does a clinician have to see before he or she in your opinion properly renders a diagnosis of sprue-like enteropathy

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associated with olmesartan?

MR. SLATER: Objection.

You can answer.

THE WITNESS: In my opinion, the most vital clinical piece of data that the gastroenterologist or primary care doctor can collect to make that diagnosis is a dechallenge, so whatever the complaint is that the patient has, if that resolves on discontinuation of -- assuming it's a GI complaint. You know, that's what we're talking about, enteropathy here --

BY MR. PARKER:

Q. Yes, sir.

A. -- not pain in my earlobe.

Q. I am not trying to be tricky. Yes, we're talking about the gut, yes, GI.

A. So if the complaints improved following cessation of olmesartan, I would say that that's

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strong evidence that the patient had olmesartan enteropathy.

Q. So there -- it can be -- any GI complaint is worthy of this diagnosis provided it goes away when you stop taking olmesartan?

A. "Goes away" is a strong -- a strong term. "Improves" is the word I would use. But there are different levels of certainty that one can have. For instance, in the patient who has severe weight loss and diarrhea as originally described by Rubio-Tapia, who has a biopsy that shows total villous atrophy, who has negative serologic testing for celiac disease, then is taken off olmesartan, the symptoms improve and the biopsy resolves, well, I've just described for you a case that is, you know, hundred percent, locked, that's what it is and it would be crazy to think otherwise. And -- in my opinion.

And in the real world, as physicians are seeing more and more of

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this, they're thinking about it sooner, so if I -- if someone goes to a physician now and says, I have -- I have nausea and vomiting and it's been for the last several months, and the physician sees that the patient is on olmesartan, from my interaction with treating physicians -- and I'm not one -- a lot of them are switching antihypertensives at that point; and I would think if that patient improved, that is good evidence of olmesartan-induced injury if that's the only change that was made.

Q. Let me go back -- and that's an important qualification.

A. Yeah.

Q. Let me come back to my question. My question is, what are the clinical features that have to be present, if any, before one gets the label?

And the first part of that answer, you said, well, they have to have dechallenge. Let me make sure I'm

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understanding. If someone were to come in and their only complaint is abdominal pain, there is no biopsy evidence of any villi loss, there's no complaint of diarrhea, they have not vomited, and the GI doctor says stop the olmesartan and their abdominal pain goes away in three days, does that person get the diagnosis of sprue-like enteropathy associated with olmesartan?

MR. SLATER: Objection to the form.

You can answer.

THE WITNESS: Well, the case you've just described to me is a nonclassical case --

MR. PARKER: Okay.

THE WITNESS: -- whether that person had injury due to olmesartan causing their abdominal pain, that, I would conclude to be fairly likely.

Whether they had sprue-like enteropathy is a different

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question and I'm not sure that I would put that particular label on it.

BY MR. PARKER:

Q. And that's what I'm trying to drive at. What do you have to have when you come into the doctor, what complaints, what findings by the doctor do you have to have, before, as you put it, the label goes on the patient?

MR. SLATER: Objection to the form of the question; foundation.

You can answer.

MR. PARKER: And if this is outside your area of expertise, just tell me and I'll move on, but I thought you said you felt comfortable answering the question.

MR. SLATER: And objection to that lead-in just now.

You can answer.

THE WITNESS: Well, I think

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it's really at the judgment of the treating physician.

BY MR. PARKER:

Q. So it can be anything if in the judgment of the treating physician -- something as abdominal pain for a couple days, in that physician's mind, that can qualify for a label of sprue-like enteropathy associated with olmesartan?

A. I think that you would have more definite and less definite cases and I think if you are the treating physician, your interest is the results; and if someone had minimal abdominal pain for three -- you know, for a few days and stopped taking olmesartan and they improved, I would not personally find that to be a very plausible case of sprue-like enteropathy.

But if you're trying to whittle -- you know, kind of get to the exact criteria, I don't think that we're there yet. I don't think that we have -- we've seen a fairly wide presentation as

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far as both symptoms and histopathology and a lot of it has been very serious. So it's not just, you know, a couple days of mild pain. It's -- we've seen some, as you're aware, very significant -- significantly ill patients.

And so I -- in my experience at Columbia anyway, the patients who I've seen labeled as sprue-like enteropathy, there's not been one of them that I've doubted the diagnosis and it hasn't been a specific point that, oh, because of -- because of X, then Y. It's been, you know, taking into account the entirety of the clinical picture.

Q. I think, however, Doctor, what -- in answer to my question about what are the clinical criteria, I think you're telling me we're not there yet in the medical community. Am I correct?

MR. SLATER: Objection; mischaracterization.

You can answer.

THE WITNESS: Well, I'm

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saying that there are varied clinical presentations and varied pathologic presentations; and, therefore, it requires the patient's doctor to make a reasonable assessment based on the entire clinical picture.

BY MR. PARKER:

Q. Let me approach it this way: Doctor, if we went into the medical text, I would be able to find the criteria for diagnosing celiac disease; correct?

A. Yes.

Q. If I went into the medical text, I could find the criteria for diagnosing autoimmune enteropathy; correct?

A. You could find some listings of criteria.

Q. If I were to go into --

A. May I make a point?

Q. Sure, yes. As long as it's answering my question.

A. Okay. I think that

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physicians diagnosing autoimmune enteropathy and if you were to go looking through the literature for -- and speaking to experts about how to do that, it often does mimic to some extent the process that a physician must go through to diagnose olmesartan enteropathy. There can be various histologic presentations, various clinical presentations. There are some antibodies that are used in the diagnosis of autoimmune enteropathy that are not positive all the time.

So it still requires clinical judgment.

Q. My question, however, is, if I went into the medical literature, would I not find statements as to what must be present within the range of variability, what must be present before a patient is labeled as having autoimmune enteropathy?

MR. SLATER: Objection. This has been asked and answered.

You can answer.

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THE WITNESS: I'm not sure that you would find universally agreed upon criteria to that extent. You would certainly find people who have suggested criteria. I couldn't say that they're universally agreed upon by experts and I wouldn't say that every patient who's been labeled with that would have fit that specific set of criteria.

BY MR. PARKER:

Q. Same question for collagenous sprue: Are there not recognized criteria for diagnosing collagenous sprue?

MR. SLATER: Objection.

You can answer.

THE WITNESS: Collagenous sprue is a bit of a more complex topic because it can occur secondary to another insult, such as celiac disease or olmesartan, or it can be what we refer to as

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primary or idiopathic collagenous sprue.

As far as the diagnostic criteria for it, there's no universally regarded pathologic criteria.

BY MR. PARKER:

Q. What about clinical?

A. There are characteristic findings, but I'm -- again, I would say that I don't believe that there is a very specific set of criteria that's agreed to by -- by the majority of experts.

Q. Same question for tropical sprue -- I'm sorry. You --

A. Collagenous sprue, just to get a little bit more into the weeds on this, if I may, it depends how precise you want to get with the criteria.

Thickened subepithelial collagen layer is a criteria, but I could also say, well, how thick is thickened and we as a medical community haven't really answered that question, so that's

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where I'm saying that there are variabilities here.

And so you asked the question of tropical sprue?

Q. Yes, sir, same question.

A. Okay. And you're asking about clinical and pathologic --

Q. Are there diagnostic criteria, clinical and/or pathologic -- if it happens to be a pathologic diagnosis -- for making the diagnosis of tropical sprue recognized in the medical literature?

MR. SLATER: Objection.

You can answer.

THE WITNESS: There certainly are sets of findings that would be expected in tropical sprue. The most important criteria for tropical sprue would be response to antibiotics as well as the clinical history of travel to an endemic area.

So there are criteria. A

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physician needs to apply them thoughtfully to actually make that diagnosis.

BY MR. PARKER:

Q. I'm sure that's true for all these conditions.

A. These ones, yes.

Q. Okay. One other one that comes to mind --

A. May I make a point?

Q. As long as it's responsive.

A. Okay. I suppose I'm clarifying these issues because I -- I want to differentiate these somewhat unusual diseases or at least uncommon diseases from something like hypertension, where if I say what's the criteria for hypertension, it's X number of blood pressure readings of X. It's extremely simple.

You know, if someone has, you know, for instance, a hemoglobin A1C over a certain level, they have diabetes. That's it. You're done.

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Whereas, opposed to, these are complex clinicopathologic entities and, you know, although there are characteristic findings clinically and pathologically, they often require a lot more thought and application of differential diagnosis than something straightforward like hypertension or diabetes.

Q. Doctor, from time to time, professional organizations like the American College of Gastroenterology gets together a group of smart people and they publish diagnostic criteria for various disorders; correct?

A. Yes.

Q. Does the College of American Pathologists do the same?

A. The CAP, College of American Pathologists, produces guidelines for cancer diagnoses. They wouldn't have a set of criteria for something -- for an inflammatory disorder such as the ones we're discussing.

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Q. Are you a member of a national medical society?
A. Yes. I'm a member of the College of American Pathologists and the U.S. and Canadian Academy of Pathology, also the Rodger C. Haggitt GI Pathology Society.
Q. Do any of those other three that you've just mentioned -- you've talked about CAP -- issue pathologic criteria for gastrointestinal disorders?
A. The Haggitt Society does from time to time.
Q. Okay. And certainly I think you said the American College of Gastroenterology does.
A. I have seen -- yes.
Q. And would you agree with me that no professional association to this day has published any criteria for diagnosing, either on a clinical level or a pathologic level, sprue-like enteropathy associated with taking olmesartan?

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MR. SLATER: Objection.
You can answer.
THE WITNESS: I would agree that I haven't seen such a document. And I would also say that -- actually, I think that finishes my answer.
BY MR. PARKER:
Q. Doctor, we've used the word a couple times this morning, but not defined it. Define for me enteropathy.
A. Enteropathy is injury to the intestines, the small intestine specifically.
Q. Does it have to be inflammatory injury?
A. It is usually inflammatory.
Q. Does -- when you say someone has enteropathy, does it include diarrhea?
A. That would be an example of one of the symptoms that would be associated with a patient who has enteropathy.

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Q. What about malabsorption?
A. That's another example of one of the clinical symptoms that one can see.
Q. But I take it you can have enteropathy without diarrhea; is that correct?
A. Yes.
Q. Can you have enteropathy without malabsorption?
A. Yes, I believe so.
Q. If -- and then what symptoms do you have if you have enteropathy, but you have not developed symptoms of diarrhea and, I'll add one, vomiting? Can you have enteropathy without vomiting?
A. Yeah, I think the clinical findings associated with enteropathy are potentially fairly broad. You've mentioned I think some of the more common ones, nausea, vomiting, diarrhea, malabsorption.
I would also not be

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surprised to see pain, either abdominal or lower. We've seen reports of fecal incontinence. Fatigue certainly is a common one. There have been reports of patients with suspected enteropathy who have had perforation of the colon. You could have various vitamin or mineral deficiencies. You could have -- subsequent to that, you could have bone or skin or hair changes. You could have mood changes.
So those are -- you know, I'm giving you examples in addition to the ones that you have mentioned. I can't swear that I've remembered everything, but these are some things that one can see.
Q. And when you say these are some things that you can see, you're talking about symptoms that are seen in patients who have been pathologically diagnosed as having enteropathy?
MR. SLATER: Objection.
You can answer.

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THE WITNESS: Patients who have been deemed to have enteropathy on the basis of their physician's assessment.
BY MR. PARKER:
Q. Is enteropathy ultimately a pathologic diagnosis, the evidence of inflammation in the small bowel?
A. I think that that evidence is certainly highly supportive. I think in certain instances in which you don't have that evidence, but you have other strong clinical evidence, I think it would be reasonable to make the diagnosis even in the absence of a biopsy.
Q. Does villous atrophy cause diarrhea?
A. Villous atrophy likely does cause diarrhea as we understand it scientifically because --
Q. How?
A. Well, it gets back to the purpose of what the villi -- why do we have villi, why did we evolve to have

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villi, and the reason why is because they increase the surface area for the absorption of nutrients.
So if you have the tube of the intestine, you have the villi protruding up, they're fingerlike projections; and if you can imagine a tube with all of these fingerlike projections, that has much more surface area than a flat tube.
And so when you have villous atrophy, you do have this flatness of the mucosa. That reduces the absorption of nutrients and therefore you would have looser stools more frequently.
Q. How does the increased concentrations of nutrients in the small bowel produce diarrhea? I'm not following that.
A. Okay. Well, let's go a little further in the GI tract and go into the colon. What does the colon do? The colon mainly reabsorbs water from stool, which is why you have formed

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stools, is because the colon has reabsorbed water.
If you're not absorbing the nutrients, fats and other nutrients, more proximally, your stool is entering your colon more -- in a more liquid format and the colon is less able to reabsorb all the water -- you'll never reabsorb all the water, but it absorbs less, and thus you have more watery stools.
Q. So greater concentrations of nutrients in the small bowel that have not passed through the villi, as you would want them to happen, you're explaining to me, causes the colon not to be able to absorb water, as is its function, thus producing diarrhea?
MR. SLATER: Objection.
You can answer.
THE WITNESS: Well, to have a more complex stool substance entering the colon than what you would like, that makes digestion of -- or reabsorption of the water

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more difficult for the colon and thus you have more voluminous stool, which will be more watery; and if you don't -- if you have malabsorption, you're not absorbing your fats, you'll also have fat in the stool.
BY MR. PARKER:
Q. Does diarrhea cause villous atrophy?
A. Does diarrhea cause villous atrophy.
In my opinion, that would be reversing the chicken and the egg. I couldn't swear to you that there couldn't be an example of someone, you know -- let me not speculate here and let me leave my answer as, no, I don't -- I would generally consider villous atrophy the cause of the diarrhea, not diarrhea the cause of the villous atrophy.
Q. How do physicians, pathologists or clinicians, determine if someone has experienced malabsorption?

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A. This is not a pathologic diagnosis. This is a clinical diagnosis based on weight loss and also potentially the composition of the stool.
Q. And what would you look to in the stool to determine whether the person has -- the patient has experienced malabsorption?
A. My understanding of it would be, fecal fat would be the cardinal -- or the most commonly used test to determine that.
Q. So you -- if you saw increased deposits of fat in the stool, you could infer that they had experienced malabsorption; is that correct?
A. I'm not a gastroenterologist, so I --
Q. Okay. If that's --
MR. SLATER: Don't interrupt. Let him finish.
MR. PARKER: Okay.
THE WITNESS: Yeah, I think -- I'd prefer not to answer that

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question because it's not my specific --
MR. PARKER: See, I was helping him. I was helping him.
BY MR. PARKER:
Q. Okay.
We talked earlier about you attending a medical conference or a meeting of some sorts at Columbia where someone explained what the soon-to-be paper was going to report from the Mayo Clinic.
You recall that?
A. I do.
Q. Okay.
Before you prepared your report in this case on November 30th, a report that concludes that the reliable evidence has demonstrated to your satisfaction, to a reasonable degree of medical probability, that olmesartan causes sprue-like enteropathy in the general population -- that's your conclusion, correct, of your report?

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MR. SLATER: Objection.
You can answer.
THE WITNESS: I'd like to see if I used the term "general population."
MR. PARKER: Oh, sure. Sure.
(Pause.)
THE WITNESS: I don't see that particular phrase, "general population," but I would be happy to answer your question as I -- as I see it, which is, I believe, to a reasonable degree of medical certainty, that in some patients, olmesartan causes enteropathy.
BY MR. PARKER:
Q. What you seem to be saying is that on a case-by-case basis, I have determined that olmesartan is the explanation for why someone has enteropathy; correct?
MR. SLATER: Objection.
You can answer.

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THE WITNESS: That would only be part of what I'm saying.
BY MR. PARKER:
Q. Then what have I left out?
A. Okay. What you just said characterizes my clinical experience fairly, I would say, but it doesn't touch the literature at all where we've seen about a hundred cases that have been reported in the peer-reviewed literature that follow similar -- similar -- that have similar findings.
And so that, of course, also plays into my thinking and we've seen epidemiological studies from France which also play into my thinking. So I do -- as I say, I believe in some patients, olmesartan is the cause of their enteropathy.
Q. Other than the case by case, you mentioned then case reports, but more of them, and epidemiology, that's the totality of the evidence that you just described for me.

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MR. SLATER: Objection.
You can answer.
BY MR. PARKER:
Q. Correct?
A. Well, I would say that those are probably the most meaningful bits of data that I've accrued over my years of being aware of this topic. There are other bits of data as well, such as some in vitro studies that have been reported and discussion with colleagues, experts, both within the United States and internationally, so I -- my experience has accrued over a number of years and in different settings and largely before I was involved in this litigation.
So I would say those are the factors that have contributed to my thinking.
Q. What I'm still struggling to understand is what you understand the term "general causation" to be. So let me ask you this question: How does epidemiology play a role in your

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assessment of causation?
MR. SLATER: Objection to the form of the question.
You can answer.
THE WITNESS: Well, I think the French study for which Basson was the first author was a powerful epidemiologic study, because it did show what I would consider a profound difference between olmesartan users and users of other ARBs; and, furthermore, I was very impressed by the fact that the duration of exposure had a significant impact on the risk of outcome of enteropathy.
So I think that that -- that particular study is a piece -- and by the way, that was a huge study looking at a lot of patients -- that is a piece of the -- of my understanding and it contributes to my understanding.
BY MR. PARKER:

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Q. But I'm not understanding, sir, how a study of a population -- which is what that was. Right? It was a population study?
A. Uh-hum.
MR. SLATER: Objection.
BY MR. PARKER:
Q. How does a population study as you have described your approach to addressing the question of causation -- how does the -- a population study weigh into your calculus?
MR. SLATER: Objection; asked and answered.
You can answer again.
THE WITNESS: It's a piece of the -- it's a piece of the picture.
BY MR. PARKER:
Q. And as you -- the piece of the picture are, individual or a number of case reports weigh more heavily in that calculus than epidemiological data?
MR. SLATER: Objection.

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You can answer.
THE WITNESS: I would say that answer really depends on how frequent an event we're talking about.
I think if we're talking about heart attacks, for instance, if I were to say case reports of heart attacks and the cases of heart attack that I've seen at autopsy weigh equally or more than epidemiologic data on heart attack, that would be a very invalid and actually ridiculous statement to make.
I think if we're talking about an uncommon event -- and it is my belief that olmesartan enteropathy is fairly uncommon -- I think that the case reports accrued from all over the world in peer-reviewed medical journals are actually extremely valuable; and, furthermore, I think the cases

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that I've experienced in my clinical practice have been incredibly instructive.

And as for epidemiologic data, it can be supportive if -- if it's a big enough study to capture what is likely to be an uncommon event.

BY MR. PARKER:

Q. Let me approach it this way, Doctor: In medical sciences, typically a rank order of the quality of the evidence as it plays upon causation, questions of causation, general causation; correct?

A. There is a hierarchy of evidence. How applicable it is to adverse drug events, I honestly don't know.

Q. All right. On the question of proving exposure to a drug and an outcome, whether it's a beneficial outcome or an adverse event outcome, would you put randomized clinical trials at the top of that list, double-blinded

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randomized clinical trials?

MR. SLATER: Can I have that question read back before he answers? I'm sorry. I spaced out on a text from someone.

- - -

(The court reporter read the pertinent part of the record.)

- - -

MR. SLATER: Objection.

You can answer.

THE WITNESS: I think, in a general sense, certainly the double-blinded RCT is a powerful study design, but it's designed generally to track one or a few specific outcomes and not necessarily all potential outcomes.

And so if something is, again, an uncommon outcome, I think the RCT can be woefully underpowered to find it, in which case, although in a general sense,

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yes, that's considered close to the pinnacle of evidence, meta-analysis being higher, there are certainly examples where it fails to be the most relevant piece of data that's been published.

BY MR. PARKER:

Q. And for purposes of my question, I'm not speaking about olmesartan. I'm speaking in a general sense. And you said, at the pinnacle, you would put meta-analysis of randomized clinical trials.

MR. SLATER: Objection.

You can answer.

THE WITNESS: I believe that's generally what people regard as the highest form of evidence.

BY MR. PARKER:

Q. And, again, all this is in a general sense. As we come down that list in terms of its value in assessing

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causality, meta RCTs, randomized clinical trials, at the next one, would you put observational studies?

MR. SLATER: Objection.

You can answer.

BY MR. PARKER:

Q. Observational epidemiological studies?

A. I'd have to review the -- there are pyramids of this sort that have been published. I'd have to review it before we get into the weeds of the cohort study versus the case-control study or what have you.

Q. Would you place case series and case reports below observational epidemiological studies, prospective or retrospective?

A. In a general -- general sense, not necessarily applicable to olmesartan and not necessarily applicable to a potentially unusual or uncommon event, I would agree that most people who rank hierarchies of evidence would list

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it as you've said.
Q. Have you ever participated in an observational epidemiological study as an investigator?
A. An observational epidemiological study. Can you define a little bit more narrowly what you mean by an observational epidemiological study?
Q. Well, let's deal with one retrospectively first. Going back into medical records and pulling out the medical records and either using a case control or a cohort design, looking at a question, but from the standpoint of the -- observing what's in the medical records.
A. Yes.
Q. Did that lead to a publication on your C.V.?
A. Yes, I believe a couple of such examples are present.
Can we do a break?
MR. PARKER: Absolutely.
MR. SLATER: Nope.

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MR. PARKER: Yes, we can.
(A recess was taken from 11:54 a.m. to 12:04 p.m.)
- - -
(Deposition Exhibit No. Lagana-4, Document Entitled "In re: Benicar (Olmesartan) Products Liability Litigation Supplemental Reliance List for Dr. Stephen M. Lagana", was marked for identification.)
- - -
BY MR. PARKER:
Q. Doctor, I'm going to do some housekeeping work before I forget to do it.
A. Sure.
Q. Exhibit No. 4 is a list of materials that were provided to me last evening by Mr. Slater titled Supplemental Reliance List for Dr. Lagana.
Can you tell me, sir, when you were -- well, let me start first, were these materials provided to you by

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counsel?
A. Some were provided by counsel. Some were papers that I had in my collection, and one or two may have been papers which I asked counsel to find because I couldn't download it at work.
Q. And were these materials that came to you either through your own efforts or through counsel after you submitted your report on November 30th?
A. Many of these papers I had read before I submitted my report. I didn't cite them directly, either because they were sort of background information or things I had read in the past, but didn't specifically rely on for the purposes of producing my report -- sorry. Does that answer the question or, if not, could you repeat it, please?
Q. It's a partial answer. Let's start with what you just partially answered.
Which of these papers -- there are 17 numbered papers and then

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there are two itemized additional materials.
A. Okay.
Q. Quite obviously, you didn't get the expert reports -- well, I shouldn't say that. Let me exclude that for the moment, so let me start again.
Let's start first with the medical literature. Which of the 17 can you now tell me under oath you had read before you submitted your report on -- on November 30th?
A. Okay. Number 4, number 10 -- oh, wait. Actually, no, that's a mistake, not 10 -- number 14. Number 15, I had skimmed. And 17 -- well, I think I had skimmed 17, but let me not say that definitively.
Q. Thank you, sir. You can put that aside -- well, before I do that, I'm sorry, let's go to the additional material.
Can you tell me under oath whether you have -- whether you read

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either one of those two referenced materials before you completed your report on November 30th?

A. Yes, I had definitely seen the FDA health safety announcement.

Q. Thank you, sir.

Let's go back to -- I was questioning you about the conference that you mentioned or the discussion at Columbia where you learned about the Mayo paper soon to be published.

Explain for me the analytic process, if there was one, from that point until you reached your conclusion that the reliable scientific evidence had proven that olmesartan was causing sprue-like enteropathy in the general population.

A. So I became aware of the association or the potential association as a -- at the time when Dr. Green, Peter Green, was speaking to a group of physicians at Columbia and he explained that, through his discussions with Dr.

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Murray, he had become aware of this association that was soon to be published.

And the -- there had been a group within our -- within the Celiac Disease Center who was working on a case series of seronegative villous atrophy. And so based on Dr. Green's discussion with Dr. Murray, researchers within the Celiac Disease Center went through the database that they collect on each patient that they see and noted that 16 -- if I recall correctly, 16 patients were on olmesartan.

So over the course of the next several months -- to put a ballpark on it, let's say six to eight months -- a number of these patients started coming back to be rebiopsied after they had discontinued olmesartan, presumably on the advice of their celiac disease doctors at Columbia.

And when I looked at the biopsies from these patients and when I

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compared those biopsies to the biopsies that they had when they were exposed to olmesartan, I noted absolutely profound changes, including in quite a few cases the resolution of collagenous sprue. And collagenous sprue up until a few years ago had really been thought to be a frequently fatal disease.

So it was a very surprising -- surprising to see the degree of improvement and it was gratifying, too, on a professional and personal level.

And during that time, I was following the literature and reading about additional cases that were published in the literature, and we were seeing new cases at Columbia of patients being referred to us for consideration of this entity. So I was exposed to additional biopsy materials.

So I would say, you know, between six months and a year, I started to feel very confident that this is a direct -- a direct causal relationship.

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Q. Based on what you just described to me.

A. Based on the cases I observed clinically, based on the literature I reviewed, based on discussions with other physicians who had had similar -- similar experiences. Those would be the main points that I -- I based my opinion on.

Q. Doctor, you mentioned a couple times today that some or all of these 16 patients had, to use your words, remarkable improvement or resolution of their symptoms when they were instructed to stop taking olmesartan; correct?

A. Some of them, yes, that I -- some of them that I am -- that I'm personally aware of, some of them, yes.

Q. And are these --

A. May I make a clarification?

Q. Sure.

A. I believe in the paper that was published based on those patients and others, the DeGaetani, et al that's in

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our reference list, I believe all of the patients improved, but I would personally not say I -- I don't have personal knowledge of every one of those patients.

Q. And that was my next point. In that paper, what they reported is, there were two other important things that were done for those patients: They had improvement on steroids and they had improvement on immunosuppressants; correct?

MR. SLATER: Objection.

You can answer.

THE WITNESS: I do know some of them got steroids and improved on steroids. I would have to look -- you used the word "all." I don't know. I'd have to check, but --

MR. PARKER: Let's take a look at it.

THE WITNESS: Okay.

BY MR. PARKER:

Q. By the way, pull out your report, sir. I just want to make sure I'm understanding. I don't recall you referencing this in your paper. You said that you had referenced this --

A. Referencing DeGaetani?

Q. Yes, sir.

- - -

(Deposition Exhibit No. Lagana-5, 2013 Article "Villous Atrophy and Negative Celiac Serology: A Diagnostic and Therapeutic Dilemma" by DeGaetani, et al, was marked for identification.)

- - -

(Pause.)

BY MR. PARKER:

Q. Am I correct?

A. Okay. Yeah, that's correct.

Q. Okay. Well, fortunately, I have a copy.

A. Okay.

Q. So Exhibit No. 5 is the result of the work that was done that you just described which was instrumental in you reaching your causation opinion; correct?

A. This is a piece of the picture.

Q. Fair enough.

Now, to the point you and I were discussing before, just so I'm understanding, this as described was an effort by your colleagues -- and you were not, by the way, a co-author of this paper, were you?

A. Correct, I was not.

Q. Were you invited to be a participant?

A. I was not.

Q. Did you review any of the biopsies of these people that are profiled here?

A. I reviewed a number of biopsies of patients that I believe were described in this paper.

Q. Okay.

And when you say a number of of the biopsies, were those biopsies that had been done before they were recontacted to come back or after they came back?

A. In a number of the patients, I have seen both the before and after.

Q. Let's turn to table 3.

A. Okay.

Q. And table 3 profiles the 16 patients out of the 72 that were determined by their records or by conversations to have taken olmesartan; is that right?

A. In table 3?

Q. Yes, sir.

A. Yep.

Q. Doctor, if you can answer this, in nowhere that I recall, but I may have missed it, is there a discussion in here about what other medications these 16 people were taking in addition to olmesartan at the time they were experiencing their diarrhea, is there, sir?